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AMERICAN JOURNAL OF PHARMACY

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

Since 1825

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E D I T O R I A L

NEED FOR MUTUAL SUPPORT

THE recent and continuing travail inflicted on the drug industry by certain agencies of government has been a traumatic and painful experience for almost everyone within the industry, and it is unfortunate that the industry itself has relatively poor facilities for correcting the false image which has been created in the minds of the American public. It is for this reason that practicing pharmacists have been urged to do everything possible in setting the record straight with consumers, and well indeed they should, since the average layman finds it difficult to differentiate the industry and the man from whom he receives his medication. Indeed, he is prone to look upon them as "brothers under the skin" and equally guilty or innocent, and not separately so. Those efforts of industry directed through the retail pharmacist as a means of improving public relations are probably the most effective means of all, for the fact remains that retail pharmacists meet and talk with more people each day than do all others having any contact whatsoever with drugs. The truth is that the reputation of the drug industry at the moment depends more on how the pharmacist handles this problem in the next year or so than upon any other single factor. By and large, pharmacists are doing yeoman service in correcting the false impression which has been created, but much still remains to be done.

Retail pharmacists, too, have their serious problems, today, and such things as the mail order prescription business, preferential discounts given to hospitals, and the increasing number of unauthorized drug outlets are but a few. There is, furthermore, the constant attrition which is taking place on our state pharmacy acts, the recent fiasco in the District of Columbia being a shining example. In their own agonies, retail pharmacists quite properly have looked to the industry for the same kind of support which industry itself has asked of them. In some instances, it has been given but not to the degree and to the extent that it should and must be. Some drug manufacturers, for example, allegedly are providing drugs to the mail order

discount houses at even lower prices than the retail pharmacist can purchase them. This is but one example of industry's failure to support those whose support it wishes.

The time has come when both industry and practicing pharmacists must face the facts concerning their mutual survival. *The private enterprise system in the manufacture and distribution of drugs is irrevocably tied to the private practice of medicine and pharmacy.* Those in industry who feel that they can function under the private enterprise system under a system of socialized medical care are deluding themselves. And, those in the professions of pharmacy and medicine who think that private practice can continue with the industry regimented by government controls are just as foolish. If each of us continues to seize that temporary advantage which may be ours at the expense of others, then our present system will not long endure. Each group needs the unqualified support of the other even though giving it poses a calculated risk. In recent months, it seems that we have been so concerned in protecting ourselves that we have given little or no thought to the problems of others in our field. This preoccupation with our own immediate problems and little or no attention to the equally serious problems of our pharmaceutical brethren makes it easy for those who seek to destroy pharmacy as we presently know it.

L. F. Tice

THE PHARMACIST AND RESEARCH *

By Jack Cooper **

PHARMACY, as you all know, is not a science in itself; it is an art which draws sustenance from many sciences. Without science or the scientific method the profession which you are soon to enter would be sterile and even fraudulent. Those among you who have a feeling for history are aware of the many nostrums which passed as pharmaceuticals at the turn of the century—cures for asthma, tuberculosis, female disorders, paralysis, syphilis, and alopecia contained in the one bottle and combining a dozen plant extracts with a suitable and frequently welcome proportion of alcohol. Drug therapy has leaped forward with gigantic strides in the last thirty years and most of this progress can be credited to planned research. Potent serums and vaccines, vitamins, sedatives, anesthetics, antihistamines, sulfonamides, antibiotics, and steroids are now the agents which highlight modern treatment and which have arisen from the mind of man operating in an increasingly complex pattern of organized research.

Literature, theatre, cinema, and television have all conspired to present the research worker in a glamorous light. He is usually pictured as a rugged individualist far removed from the cares of the world, but nevertheless a restless victim of insomnia. In the middle of the night he rushes off to his test tubes, heroically lights the Bunsen burner and, with a smile of gentle self-infatuation, turns H_2O from technicolor red to technicolor green, or vice versa depending on whether it is an American or a Russian movie. To the enraptured viewer, this is indeed more exciting than differential equations but somewhat more distant from the truth. It is becoming increasingly apparent that advances in science today and most particularly in medicine are dependent upon the collaborative efforts of a large group of research workers, each possessing specialized knowledge. The chain of events involved in carrying forward the development of a drug from the initial synthesis of a few grams of the material to a group of medicinal products designed to serve a specific purpose or

* Presented May 18, 1960 to the Rho Chi Society, Temple University School of Pharmacy.

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mode of administration is a long but necessary one. The tendency of the press and organized medicine to associate progress in therapeutics with the medical profession alone is psychologically understandable but completely inaccurate. The pharmacist also has a role to play in this sequence of events but to do so he must understand the research process itself as well as the area of his potential contribution.

In a broad sense, research has been defined as the application of human intelligence in a systematic manner to a problem whose solution is not immediately available. Although this definition covers the individual worker, the informal group, and the organized team, group research should be distinguished from individual research in spite of some similarities. The need for a systematic approach to integration is not too important when applied to the lone worker but, as soon as several individuals combine to solve a problem, the need becomes paramount. The individual laboratory worker may indeed follow a careful plan of hypothesis, experiment, results, and so forth such as was taught him in his graduate work or he may follow a less rigid plan. On the other hand, in group work the guidance of a skillful director may render individual methodology less important; conversely, poor direction and research can waste talent most effectively.

The assignment of higher social or intellectual values to certain forms of research activity represents a rather naive concept on the part of some "ivory-tower" scientists who feel it necessary to imply that technological or applied research is in some way inferior to other forms of scientific research. There is undoubtedly as much poor quality in pure research as there is in applied research. The methodology applied to any type of research fits any basic definition although the techniques, apparatus, and environment may differ. The tendency to separate researchers into two groups is unnecessary and harmful since it limits their mutual understanding of related problems. The essence of science is the discovery of exact knowledge—discovery that can only result from the protracted application of the scientific method. All aspects of science are interdependent and the scientific method cannot be differentiated into mutually exclusive theoretical and practical branches. The very diversity of the pharmaceutical sciences makes it necessary for all pharmacists whether researchers or not to understand the basic structure of science as a body of knowledge and research as a systematized process of solving problems.

What type of research can we catalog as pharmaceutical? The following can probably be listed as representing the most important areas:

1. The isolation and purification of the active principles of plant and animal tissues and organs; the determination of their chemical composition and eventually their synthesis.
2. The synthesis of new compounds with the intention of discovering new drugs.
3. Research on the cultivation of medicinal plants.
4. Research on the pharmacodynamics and toxicology of drugs.
5. Research on the effects of drugs on micro-organisms as well as the utilization of micro-organisms for the production of drugs.
6. The preparation of drugs in suitable dosage forms including the development of methods for sterilizing and preserving them.
7. The biological and chemical standardization of drugs.

It is perfectly obvious that, although individual pharmacists and schools of pharmacy are active in each of these areas, in none of them can pharmacy any longer claim a monopoly. Chemists, botanists, pharmacologists, biochemists, microbiologists, and physicians by the tens of thousands are busy in these areas in full time careers. As a matter of fact, what should claim our attention is the relatively poor position of pharmacy in the ranks of the disciplines active in the development of therapeutic agents. This situation is as true in the modern pharmaceutical industry as it is in the academic world.

It is probable that the traditionalism and conservatism of the profession led to the presence of many men in our schools and professional organizations who were unreceptive of new ideas and lacked understanding of the systematic and logical basis underlying the experimental method in science. As Almroth Wright once wrote, "The ordinary man feels perfectly sure (at least he does so in his young years) that he has been endowed by Nature with a faculty of believing, and an apparatus of reasoning which never go wrong. He naturally concludes that his mind has as little need of logic as normal eyes have of spectacles."

The sluggish reaction of teachers and practitioners of pharmacy to the revolutionary implications of the discovery of the therapeutic value of the sulfonamides, the failure to understand the widening role of pharmacology in the evaluation of new drugs, and the stubborn resistance to the changing role of the dispensing pharmacist resulted in the graduation of thousands of pharmacists inadequately prepared to advance the scientific standing of their profession. The new tools, theories and principles in chemistry, physics, and the biological sciences found their way into our schools of pharmacy much too slowly. Although the function of a professional school is to advance knowledge as well as transmit it, the contributions made by our schools of pharmacy during the 1930's and 1940's are no cause for pride in our ranks.

This point of view may appear to be too harsh to many of the fine teachers who attempted to guide pharmacy along a progressive path during this period but it is necessary to recognize past mistakes in order to plan correctly for the future. It is now perfectly clear that there will be no return to manipulative techniques on the part of the dispensing pharmacist. It is equally evident that the impact of the advancing frontiers of the various sciences which make up pharmacy are forcing alteration of curricula in our pharmacy colleges. Even more important but changing less rapidly is the elevation of the quality of the work required of pharmacy students both in the laboratory and in the classroom. There is no logic other than the foolish acceptance of outmoded custom which permits the continuation of lower standards of performance by students in schools of pharmacy when compared to students taking equivalent courses in other schools.

It is revealing no secret to state that pharmacists no longer play the important role in the pharmaceutical industry which normally would be expected of them. Although many individual pharmacists hold executive or technical positions, the proportion of such men and women in the industry is much too small when consideration is given to the fact that in principle they should be ideal candidates. There is no doubt that until recently training for industrial pharmacy at the necessary technological level was simply not available in our schools of pharmacy. In large part this weakness stemmed from the absence of suitable research programs in these institutions.

Although admitting this unhealthy situation, some critics blame it upon the shortsightedness of the pharmaceutical industry in failing

to encourage and support research in academic pharmacy. There is probably more than a grain of truth in this charge and in some respects the industry has also paid a price for this unfortunate situation. An essential element in the chain of events leading to a new drug is the research pharmacist. Creative chemists, observant pharmacologists, and critical clinicians are not enough. The patient or the physician does not employ a chemical for therapeutic purposes; he uses a pharmaceutical dosage form. The problems involved in formulating a suitable, stable dosage form capable of being routinely manufactured on high speed production equipment and safely used in one of numerous ways by the patient are complex and beyond the capabilities of the chemist or the pharmacologist. Good research pharmacists are hard to find and they are sorely missed in an industry whose very name is based upon the profession of pharmacy.

In my opinion there is an even greater weakness in the approach of industrial circles to pharmacy research as represented by the so-called "trade secret" philosophy. In this illusory world of exaggerated notions of superiority are buried all sorts of ridiculous advantages claimed to be of economic value to the holder of the secret. In their anxiety to protect such theoretical and unchecked advantages, many organizations have built a wall around their pharmacy research groups behind which are hidden unknown men holding unknown inventions close to their chests. Their ideas and practices become ingrown, fail to be subjected to the fine comb of outside analysis and criticism and grow stale from lack of intercourse with other men and other ideas. These pharmaceutical prisoners do not speak nor do they publish and no forum provides an opportunity to praise or ridicule their accomplishments.

It is dubious indeed that such a restrictive policy actually is beneficial to those who indulge in the practice. Even more dubious is the courage of the research pharmacists who tolerate it. As with other disciplines in the industry the equity of the company can be protected by patents on compositions, processes, and equipment as well as by ever continuing progress without completely restricting the communicative lifeblood of its research pharmacists.

At this point in the discussion it is only fair to reverse the pessimistic overtones of my remarks and emphasize vigorously that the future for pharmacy research is becoming brighter at an accelerating pace. The steady growth in graduate programs and research

facilities in our schools of pharmacy, the rapid expansion of pharmacy staff and laboratories in the pharmaceutical industry, and the opportunities provided by the establishment of the Section on Industrial Pharmacy of the American Pharmaceutical Association are welcome omens of an improving scene. One of the important stimuli to change has been a new awareness of the evidence in the form of sustained-release preparations, depot injections, and superior emulsified dermatologic medications that the results of pharmacy research can be of therapeutic as well as pharmaceutic importance. It is also becoming increasingly apparent that the area of pharmacy development research, i.e., the solution of problems in large scale manufacturing operations has been neglected and requires reorientation and expansion. The high potency and specific effects of our new drugs confer a great responsibility upon the technological ability of those who must organize its routine preparation and testing.

Whether he is actually engaged in some form of research activity or not, every practicing pharmacist must be aware of the research process and its accomplishments in this field. This awareness arises from the pharmacist's academic training in the basic sciences, his laboratory experience and such external stimuli as visiting lecturers, student science clubs, and professional associations. After graduation, refresher courses, local, state, or national meetings and journals are available. Failure of the graduate pharmacist to continue along these lines progressively reduces his professional ability. The knowledge accompanying the 1960 diploma will be somewhat outmoded before the class of 1965 gleefully or sadly departs from these halls of learning. What is new will have been acquired as the result of the research process at work in thousands of laboratories all over the world.

Not only the researcher but every pharmacist has a vested interest in research. He should recognize, encourage, and support this phase of the activities of his profession regardless of whether the laboratories are situated in the campus of a university or on the campus of a modern industrial complex. He should encourage his organizations to play a vital role on the financial support of good research and to act as one of the means of communication between the researcher and the members of the organization. All pharmacists profit directly and indirectly from the good research with which the future of their profession is inextricably bound—more so, in fact, than many of the commercial struggles which occupy so much of their time, energy,

and vocabularies. Just as the shift in therapeutics during the 1930's caught the profession and its schools by surprise and for over two decades left them gasping for a new foothold in the ranks of health scientists, other changes can also be expected in the years to come By advancing knowledge through research the element of unexpected change is removed and pharmacy can regain and retain its position on the health team. If we are tired of being second cousins, auxiliary technicians, or licensed tradesmen, then let us improve and publicize our scientific contributions to the end product of our labors, i.e., the development, preparation, and distribution of effective drugs.

I have earlier tried to picture the glamorized version of the modern researcher. In actuality he would be difficult to pick out of a crowd. The top-notch research worker is an individual with imagination and bold ideas but these traits are matched by the perseverance and concentration necessary to follow an idea through to the sometimes bitter end. Enthusiasm and spirit are essential but not to the degree that he refuses to face unpleasant facts. The good researcher knows how to pursue the main objective of his research and not be detoured into pleasant but unprofitable bypaths. He must know when to stop because there may come a time in any project when further work is unprofitable. Most difficult but sweetest of all is the new problem that faces him upon the completion of the old.

COMPOSITION STUDIES ON TOBACCO. XI

High Molecular Weight, Cyclic Hydrocarbons From Flue-Cured Leaves

By R. L. Stedman,* A. P. Swain,* W. Rusaniwskyj,* and J. G. Bendoraitis **

Introduction

DURING preliminary work in a previous study (Stedman and Rusaniwskyj, 1959), hydrocarbon mixtures were isolated from Type 12 leaves which showed infrared spectra having more extensive chain branching and shorter unbroken methylene chains than those expected for the aliphatic n- and iso-paraffins (Carruthers and Johnstone, 1959; Johnstone and Plimmer, 1959) known to be in tobacco. Thus, the presence of highly branched hydrocarbons was indicated. The present report concerns the isolation from flue-cured leaves of branched cyclic hydrocarbon mixtures which superficially resemble the higher cycloparaffins of petroleum.

Methods and Results

Isolation

Cured, unaged, ground Type 12 leaf webs (39.6 kg) were extracted with Skellysolve B [2] as previously described (Dymicky and Stedman, 1959). The Skellysolve extract was reduced in volume, refrigerated, and filtered. The filtrate was then extracted with 90 per cent methanol, giving 1443 g of methanol-insoluble material (S3, Figure 1). S3 was chromatographed batchwise on Merck acid-washed alumina (activated at 150° C. for 15 hours) and the columns

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** Socony-Mobil Oil Company, Paulsboro, New Jersey.

1. Eastern Utilization Research and Development Division, Agricultural Research Service, United States Department of Agriculture. Address all inquiries to this Division.

2. Mention of a specific commercial product does not constitute endorsement by the United States Department of Agriculture. This solvent contained approximately 0.0008 per cent non-volatile residue (b p $>$ 73° C.).

were developed by a flowing technique. Sixteen liters petroleum ether (on four columns) eluted a light brown, semisolid material (S3A); subsequently, 20 liters petroleum ether removed a viscous oil containing pale yellow needles (S3B). The solvent was changed to petroleum ether-benzene, 1:1, and two fractions were collected, the first with 16 liters (S3C) and the second with 32 liters (S3D). Subsequently, 63 liters benzene eluted S3E.

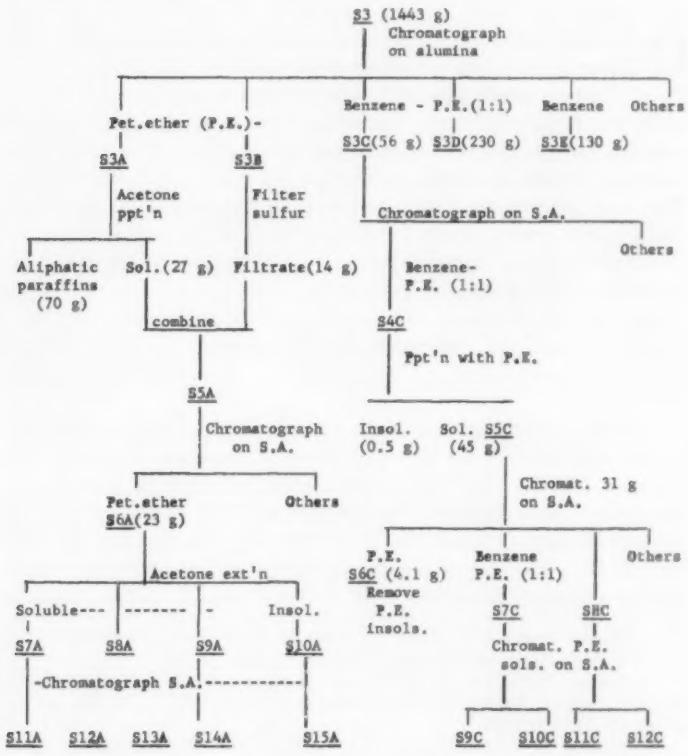

FIGURE 1

ISOLATION OF MIXTURES CONTAINING HIGH MOLECULAR WEIGHT, CYCLIC HYDROCARBONS

S3A and S3B. S3A was precipitated with acetone to give an insoluble portion containing mostly aliphatic paraffinic hydrocarbons, and a soluble portion. A small amount of petroleum ether was added to S3B and the yellow crystals (1.3 g) were filtered off. The filtrate was then pooled with the soluble portion from S3A, giving S5A. The yellow crystals were subjected to elemental analysis after recrystallization and showed 100 per cent sulfur.

Thirty-eight g of S5A were chromatographed on activated silicic acid (Mallinckrodt). One and two-thirds liters petroleum ether eluted 23 g of a pale yellow, viscous oil n^{24}_D 1.4745, (S6A) and the other components on the column were eluted with solvents and mixtures thereof of increasing polarity. The infrared spectrum of S6A indicated the presence of hydrocarbon(s) with slight unsaturation at 11.25μ ($R_1R_2C{=}CH_2$), extensive branching and unbroken methylene chains of moderate length. S6A was then extracted with acetone four times, yielding three extracts (S7A, n^{21}_D 1.4710; S8A, n^{21}_D 1.4723; S9A, n^{21}_D 1.4766) and an insoluble residue (S10A, n^{21}_D 1.4710), all four being similar in physical appearance.

These four fractions were each chromatographed on activated silicic acid. The columns containing S7A (5.9 g), S9A (2.5 g), S10A (8.2 g) and one-half (2.9 g) of S8A were run at 0° C. using the apparatus described by Clements (1958), and the other half of S8A was run at room temperature. In each case, the bulk of the sample was obtained in a number of fractions eluted with 0.4-1.0 liter petroleum ether and the nature of these eluates was quite similar, appearing as a semisolid white wax, a free flowing, clear, colorless oil or a mixture of the two. The columns were then rinsed with diethyl ether and the remaining material (10-30 per cent of total) was eluted; no effort was made to identify this material. In general, the patterns of elution of S8A at 0° C. and room temperature were not strikingly different.

Several samples of the above semisolid wax and clear oils were selected for further study: S11A (oil from S7a); S12A (oil from S8A chromatographed at room temperature); S13A (oil from S8A eluted from chromatography at 0° C.); S14A (oil from S9A); S15A (wax from S10A). Further work on these substances is described below.

S3C and S3D. S3C was chromatographed on activated silicic acid. Elution with 1:1 petroleum ether-benzene removed 45.5 g of a

thick, viscous, pale yellow oil (S4C). By precipitation with petroleum ether at —14° C., approximately 0.5 g of a solid was removed from S4C; the solid melted at 59°-63° C. and showed the infrared spectral characteristics of a long chain, aliphatic ester. The filtrate (S5C) from this precipitation yielded a viscous oil the infrared spectrum of which exhibited a highly branched hydrocarbon structure having traces of unsaturation ($R_1R_2C=CH_2$) and a carbonyl component.

An aliquot (31 g) of S5C was chromatographed on activated silicic acid. Petroleum ether (1.0 liter) eluted 4.1 g of a viscous, almost semisolid oil (S6C). Further amounts of this solvent eluted another 1.2 g of a similar oil from the column in two fractions. Benzene-petroleum ether, 1:1, then removed 11 g of a resin-like slightly brown material (S7C) followed by 6.5 g of a darker resin (S8C).

Fractions S6C, S7C, and S8C were found to contain small amounts of a tacky material insoluble in hot petroleum ether which was filtered off. The filtrate from S6C was evaporated to a pale yellow, semisolid resin which was used in the analytical work described below. The filtrates from S7C and S8C were evaporated and aliquots of each of the residues chromatographed on silicic acid. From 6.2 g of S7C were obtained several fractions, of which two were selected for further study: S9C (2.5 g) eluted by 10 per cent benzene in petroleum ether and S10C (2.2 g) removed by 75 per cent ethyl ether in benzene. Similarly, S8C (4.3 g) yielded a number of fractions including S11C (1.3 g eluted by 10 per cent benzene in petroleum ether) and S12C (0.7 g removed by 10-50 per cent ethyl ether in benzene). S6C and S9-12C were studied in detail as described below.

S3D and S3E. After removal from S3D and S3E of small amounts of materials insoluble at —14° C., the filtrates were repeatedly chromatographed on silicic acid. Several fractions were obtained which were similar to those isolated from the above fractions and discussed in detail below.

Analytical Data

Vapor phase chromatography. Several of the fractions were screened by this procedure to determine purity. A number of experimental conditions were employed. S11A, S12A, and S13A were each found to have eight or more components, and several components

having similar retention times were found in each fraction. S14A showed one distinct peak of low retention time, but indications of slowly eluted high boiling components were observed. The findings with S15A were difficult to evaluate and purity could not be claimed. S6C gave one major peak and possibly two minor constituents at 240° C.

Microanalyses. The appearances, melting ranges, elemental analyses, average molecular weights (Rast), empirical formulas and refractive indices of the fractions are shown in table 1. It should be emphasized that all fractions were mixtures and that the data represent mean values. S15A was the only fraction giving a total of 100 per cent carbon and hydrogen, although the amounts of oxygen present in S11A, S12A, and S6C were too small to account for one atom of oxygen per molecule based on the molecular weight by the Rast procedure. The carbon:hydrogen ratios of all fractions suggested the presence of possible cyclization, unsaturation or aromaticity; the fractions in the "C" series showed a much higher degree of these characteristics than the "A" series.

TABLE 1.

PROPERTIES OF ISOLATED FRACTIONS

Fract.	*Appearance*	*Melt. Range (° C.)*	*Microanalys. (%)**			*Mol. Wt.*	*Empirical Formula****	$n^{20}D$
			C	*H*	*C + H*			
S11A	Colorless oil	25-30	84.63	13.66	98.29	530	$C_{37}H_{72}O_{0.56}$	1.4715
S12A	Colorless oil	25-30	83.80	13.23	97.03	515	$C_{36}H_{68}O_{0.96}$	1.4740
S13A	Colorless oil	20-25	83.81	13.38	97.19	—	—	1.4764
S14A	Colorless oil	20-25	84.94	13.50	98.44	—	—	1.4787
S15A	Opaque wax	35-40	86.18	13.94	100.12	515	$C_{37}H_{72}$	1.4814
S6C**	Yellow resin	—	86.51	11.84	98.35	560	$C_{40}H_{66}O_{0.58}$	1.5307
S9C	Yellow resin	—	83.80	11.02	94.82	525	$C_{37}H_{57}O_{1.7}$	1.5320
S10C	Brown resin	—	77.78	10.36	88.14	760	$C_{49}H_{78}O_{5.6}$	—
S11C	Yellow resin	—	77.33	10.97	88.30	730	$C_{47}H_{79}O_{5.3}$	1.5310
S12C	Brown resin	—	74.55	10.33	84.88	900	$C_{56}H_{92}O_{8.6}$	—

* All fractions were negative for N, S and halogen.

** Showed $[\alpha]^{28}D$-9.8 (c, 2.12 in chloroform). Optical rotations on other samples were not determined.

*** Assuming the difference between (C + H) values and 100 per cent is oxygen. As an alternate procedure, the empirical formulas may be corrected for this difference in the case of hydrocarbons having trace amounts of oxygen or other contaminants (Zechmeister and Sandoval, 1946). Such corrections give formulas of $C_{38}H_{74}$, $C_{37}H_{70}$, and $C_{41}H_{68}$ for S11A, S12A, and S6C, respectively.

Oxidation and reduction. Results of tests with concentrated sulfuric acid, potassium permanganate in acetone and bromine in carbon tetrachloride are detailed in table 2. S6C and S15A were insoluble and relatively unreactive with concentrated sulfuric acid; fraction S11C gave a reaction typical of organic compounds attacked by this reagent. All tested fractions decolorized bromine (at least in part) by a substitution reaction. Microhydrogenation (in dioxane using palladium on carbon as catalyst) showed less than one double bond per molecule based on the Rast values.

Infrared spectra. The spectra of all samples showed the presence of a rather highly branched hydrocarbon skeleton containing no or slight unsaturation and amounts of oxygen-containing groups varying from a trace (S15A) to a considerable quantity (S12C). Branching was indicated by strong absorption at 7.23μ (CH_3—) relative to 6.82μ (— CH_2 — and CH_3 —) combined with weak 13.7μ

TABLE 2.

PROPERTIES OF ISOLATED FRACTIONS

Fract.	*Conc. H_2SO_4 Color**	*Solub.*	*$KMnO_4$***	*Br_2 in CCl_4****	*Microhydrogenation*****
S11A	R-O	Insol.	O	+	0.50
S12A	——	——	—	—	0.24
S13A	R-O	Sl. sol.	±	++	——
S15A	S1Y	Insol.	O	+	0.025
S6C	S1Y	Insol.	O	+++	0.40
S9C	R-B	Insol.	±	—	0.42
S10C	——	——	—	—	0.23
S11C	B1	Sol.	—	—	0.32
S12C	——	——	—	—	0.56

* R-O = red-orange, S1Y = slightly yellow, R-B = red-brown, B1 = black.
** ± = Slight decolorization in 15 minutes, O = no change in 15 hours.
*** Speed of decolorization: + = slowest, +++ = fastest. All fractions evolved HBr (litmus test).
**** Number of double bonds per molecule.

(unbroken — CH_2 — chains) bands in all samples.[3] Aromatic nuclei were absent. Figure 2 shows the spectrum of S15A (in carbon disulfide), which was representative of those fractions having no or small amounts of oxygenated components; figure 3 shows the bands at 7.23 and 6.82μ (in carbon tetrachloride) for S15A. Table 3 gives the ratios of absorptivities at 6.82 and 7.32μ to illustrate the degree of chain branching in all fractions.

The oxygen-containing groups were characterized by broad bands in the 5.7-6.0μ region, including some possible α, β-unsaturated

TABLE 3.

CHAIN BRANCHING IN VARIOUS FRACTIONS BY INFRARED SPECTRAL ANALYSIS

Fraction	*Ratio absorp. 7.23μ* / absorp. 6.82μ*
S11A	0.609
S12A	0.679
S13A	0.719
S14A	0.715
S15A	0.678
S6C	0.894
S9C	0.908
S10C	1.06
S11C	0.946
S12C	1.12

* All spectra determined in carbon tetrachloride. Absorp. = absorptivity.

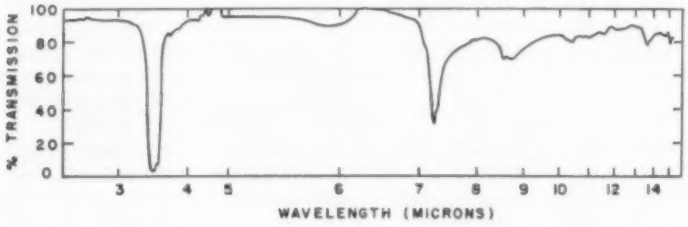

FIGURE 2

INFRARED SPECTRUM OF S15A. THREE PER CENT SOLUTION IN CARBON DISULFIDE

3. For various reasons, the 7.23μ band may frequently be stronger than the 6.82μ band as in certain of the above fractions. Aliphatic n-paraffins of tobacco have $\frac{\text{absorb. } 7.23\mu}{\text{absorb. } 6.82\mu}$ values of about 0.218.

carbonyl in at least two fractions (S6C and S9C). In the more highly oxidized fractions, small amounts of hydroxyl absorption were noted. A tendency was observed for slow, progressive auto-oxidation on prolonged storage, even under nitrogen, of fractions in the "C" series as judged by intensification of color and increased absorptivity of the oxygen-containing groups of the infrared spectrum; this tendency was not as marked in the "A" series of fractions and might have been a reflection of degree of chain branching or cyclization in the two series. A similar pattern is noted in the petroleum naphthenes.

Mass spectra. Four of the above fractions (S11A, S15A, S6C, and S6D) were submitted to mass spectrometric analysis. In addition, two other fractions (123-2 and 169-21) obtained by extensive chromatography on silicic acid of S3D and S3E were also run. The essential features of the mass spectra are given in table 4.

TABLE 4.

MASS SPECTRA OF MIXTURES CONTAINING CYCLIC HYDROCARBONS FROM TYPE 12 LEAVES

Fraction	*Significant Masses in Fragment and Parent Peak Regions (m/e)**	*Components*
S11A	278,** 527, 541, 555	Naphthene-like. Mono-, di- and tricyclic constituents present.
S15A	278, 317, 331, 345 359, 527, 541, 555, 609, 623, 637, 830	Similar to S11A.
S6C	325, 393, 461, 597, 612	Naphthene-like. Tetracyclics predominate. Moderate amount of pentacyclics. Small quantities of tricyclics. Possibly some (<5 percent) iso-paraffins.
S9C	323, 391, 608, 610, 612	Naphthene-like. Tetracyclics predominate. Some tri- and pentacyclics possibly present.
169-21	323, 391, 608, 610, 612	Almost identical with S9C.
123-2	142, 156, 170, 184, 393, 421	About 50 per cent iso-paraffins (C_{20} and C_{31}) and n-paraffins (C_{10} to C_{13}). Remainder are mono- and polycyclic compounds.

* Mass spectrometer operated at 350° C./0.01 mm. Hg.; variation of ± 2 m/e in high molecular weight peak ranges (>600).

** Parent mass of neophytadiene (Gladding *et al.*, 1959).

In general, the spectra showed the presence in all fractions of hydrocarbons having cyclic structures superficially similar to the naphthenes found in petroleum. Specifically, however, the patterns of the spectra showed the components of the mixtures from tobacco to be quite unlike the cycloparaffins of petroleum. The dissimilarity was such that quantitative spectral evaluation for specific structural details by comparison with known petroleum naphthene characteristics was difficult in most instances. Despite extensive fractionation, the samples appeared to be complex mixtures.

In table 4, the major fragment and parent masses ($^{m}/_{e}$) are indicated for each fraction. Each of the samples showed a number of high molecular weight fragments. Due to the variations in $^{m}/_{e}$ values in the higher ranges, it was uncertain whether the peaks at >600 were fragments or parent masses. Comparison of these peaks with the Rast molecular weights indicated that compounds having relatively high molecular weights predominate in the fractions. The major components in fractions having less chain branching and higher C:H ratios (S11A, S15A) were one-, two- and three-ring structures. Those samples showing lower C:H ratios consisted mainly of tetracyclic constituents in combination with some three- and five-ring compounds. Only one sample (123-2) gave a spectrum which, when evaluated according to a scheme devised for quantitative analysis of petroleum hydrocarbons, yielded rational values. This sample showed about fifty per cent iso-paraffins (approximately C_{31-33}) and n-paraffins (C_{10-15}), the remainder being ring compounds with monocyclics predominating.

Discussion

Of the fractions studied completely, all were mixtures of compounds having high molecular weight, saturated, cyclic hydrocarbon structures therein. Some unsaturated linkages were found in each fraction, but these were comparatively few. At most, the low level of unsaturation might have caused an error in mass spectral evaluation of one ring, but, in all probability, was too slight to be of significance in this regard. The observed large fragment or parent masses and high average molecular weights (Rast) might indicate that molecules having repeating units of polycyclic hydrocarbons linked by methylene groups or aliphatic chains exist therein. Undoubtedly, substituents consisting of methyl groups or branched alkyl

chains are also present. Although the mass spectra of the more highly oxygenated fractions, S10C, S11C, and S12C, were not examined, these mixtures appeared to be basically related to the other samples, existing perhaps, as more complex structures of greater susceptibility to oxidation; in fact, S6C through S12C could be visualized as a relatively progressive series in this respect.

As far as we are aware, cyclic, saturated hydrocarbons of this type have not been previously reported in plants, and no mixture of known, fully characterized plant constituents could fulfill the physical properties outlined above.

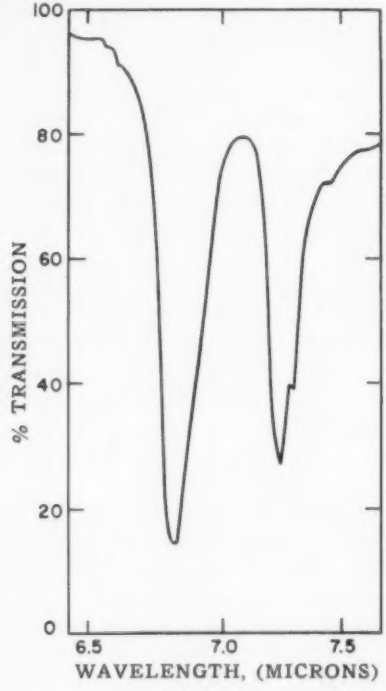

FIGURE 3

INFRARED ABSORPTION OF S15A IN THE 6.5-7.5 MICRONS REGION SHOWING DEGREE OF CHAIN BRANCHING. THREE PER CENT SOLUTION IN CARBON TETRACHLORIDE

Although the compounds are significantly unlike the petroleum naphthenes, the possibility that they are artifacts[4] has been extensively considered. The source of the compounds was not the non-volatile residues from the (petroleum-derived) extracting and chromatographic solvents for two reasons: repetition of the fractionation (on a smaller scale) using highly purified solvents essentially free of non-volatile residues resulted in the isolation of mixtures similar to the above; and the total amounts of non-volatile residues (4.9 g) in all solvents used in the above fractionation were significantly less than the estimated quantities of the mixtures isolated thus far from tobacco (greater than 40 g[5]). Perhaps part or all of the non-volatile residues carried over into the fractions; the n-paraffins from C_{10} to C_{13} in fraction 123-2 may be of such origin. Iso-paraffins in the C_{27-33} range (*cf.* $^{m}/_{e}$, 393 and 421, fraction 420-123-2) have been previously reported in tobacco. Perhaps the elemental sulfur found above was derived from the extracting solvent rather than fungicidal residues on the leaves (Weybrew, 1959).

Polymerization of tobacco olefins on chromatographic columns[6] represents another possible extraneous source. Fink *et al.* (1950) and Gallaway and Murray (1958) mentioned the effect of low temperature in reducing polymerization of olefins on chromatographic columns but gave no details; other workers have commented on

4. Another possible artifact is the deposition of residues on leaves during curing as a result of improper operation of the burners employed to provide heat. Since the isolated substances give mass spectra not identical with petroleum naphthenes, this possibility appears to be eliminated.

5. These values are based on the weights of isolated fractions which appeared similar by inspection and other physical characteristics (index of refraction, infrared spectrum, and chromatographic behavior) to those studied more intensively. Although work on the separation of S3D and S3E has not been completed, a considerable amount of resin-like material similar to S6C and S9C (as well as smaller amounts of solids similar to S15A) has been obtained from these fractions, making the above estimate quite conservative.

6 Mention should be made of the striking difference between the chromatographic patterns of tobacco extracts on acid-washed alumina and on silicic acid. The latter does not isomerize neophytadiene and appears to be a stronger adsorbent than Merck acid-washed alumina. Petroleum ether eluates from silicic acid columns contain only aliphatic paraffins and neophytadiene, the latter being obtained as an acetone-soluble, colorless, light oil. Similar eluates from acid-washed alumina columns contain aliphatic paraffins, isomerized neophytadiene, some of the cyclic paraffins, unidentified unsaturated (11.25 μ) hydrocarbons and an unidentified, dark brown oil. The acetone-solubles from such eluates are dark brown, thick oils. Repeated chromatography of the latter on silicic acid serves to separate the unsaturates from the saturated material to some degree, although traces of unsaturation usually persist.

isomerization of olefins under such conditions, including some negative findings (Saier *et al.*, 1954; Johnston *et al.*, 1948). To check this possibility, squalene (Kosak and Swinehart, 1958; Van Duuren and Schmitt, 1958) was chromatographed on acid-washed alumina and silicic acid. Although some isomerization was observed on the alumina column (but not on silicic acid), no compounds resembling the above cyclic hydrocarbons were isolated. In similar trials with neophytadiene (Rowland, 1957; Onishi *et al.*, 1958; Gladding *et al.*, 1959), only isomerization on acid-washed alumina was observed: the infrared spectral characteristics of the eluates suggested that phytadiene C (Rowland *et al.*, 1957) was the principal isomer present.

Although the isolated hydrocarbons are subject to auto-oxidation, it is felt that the more highly oxidized fractions, e.g., S10C, exist as such *in situ*. Prolonged manipulation and exposure to air of fractions having low oxygen contents, e.g., S6C, has not resulted in their altering physical appearance or infrared spectral characteristics to a degree found in the more highly oxidized samples.

At least three practical implications of the present findings are evident. First, the extreme tackiness of such fractions as S6C suggests that they may contribute to the gummy or oily characteristics of the leaf, one of the desirable quality features. Secondly, the cyclic hydrocarbons may be quite easily dehydrogenated during pyrolysis and be involved in the formation of aromatic polynuclear hydrocarbons known to be present in smoke. Thirdly, the presence of such compounds in plants may have a bearing on current theories of petroleum origin which require the postulation of mineral-catalyzed polymerization of fatty acids or olefins to explain the presence of naphthenes therein (Brooks, 1950, 1951).

The failure to separate a single compound from the above mixtures is hardly surprising since prolonged, consistent effort by many workers to fractionate the higher naphthenes in petroleum has met with only limited success.

Summary

The isolation of mixtures containing saturated, cyclic hydrocarbons from flue-cured tobacco leaves is described. The structural features of the compounds were established from microanalyses (carbon and hydrogen, catalytic hydrogenation and molecular weight); reactions to concentrated sulfuric acid and oxidizing agents;

and infrared and mass spectral characteristics. Most of the hydrocarbon mixtures exist in various degrees of oxidation and show mass spectra having fragment and parent masses in the 278-830 range; the major components of the mixtures superficially resemble the higher naphthenes of petroleum to some extent, although outstanding differences exist. The possible roles of these compounds in contributing to leaf gumminess, to the pyrolytic generation of aromatic polynuclear hydrocarbons during smoking, and to the current theory of the origin of naphthenes in petroleum were discussed.

Acknowledgments

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THE SHAKERS AS PIONEERS IN THE AMERICAN HERB AND DRUG INDUSTRY *

By Charles O. Lee **

THE religious sect known as Shakers were among the pioneer settlers of Kentucky, Ohio, and Indiana. A small number of this sect migrated from the eastern colonies but most of the early Shakers of this area were converted to the Shaker way of life by missionaries sent to the wilderness of the southwest country by the Shaker colony of Mount Lebanon, New York, about 1802.

It is stated that the success of these early missionaries in winning converts to Shakerism was attributed largely to the religious upheaval that resulted from the great Kentucky revivals that took place around 1800. The emotional fervor that was generated by these revivals was widespread and extended well up into southern Ohio. Reports indicate that the Protestant churches, especially the Methodists and Presbyterians, were greatly perturbed by the preachments of the revivalists on the subjects of sin, repentance, and the second coming of Jesus. Religion was, to most of the early log-cabin pioneers, an important matter.

The Shakers had settled for themselves, among other things, the second coming of Christ. Their missionaries could, therefore, expound the Shaker doctrine with great sincerity of faith and assurance. And, in the course of a few months, they had won many ardent converts in Ohio and Kentucky. By 1805, there were 125 Believers in Ohio. In 1811, the Union Village society, west of Lebanon, had 300 members.[1] In the decade or so before and after 1811, there were four Shaker societies established in Ohio, two in Kentucky, and one in Indiana. From about 1787 to about 1823, nineteen societies of Shakers had been founded—three in New York, four in Massachusetts, two in Maine, two in New Hampshire, and one in Connecticut. No new societies were formed after 1830.

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* This paper was presented at the annual convention of the American Pharmaceutical Association in Cincinnati, Ohio, August 14-21, 1959.

** Professor of Pharmacy, Ohio Northern University, Ada, Ohio.

1. MacLean, John P., *Shakers of Ohio*, 1907.

Melcher states that ". . . the period of greatest prosperity and influence for the Shakers came, roughly speaking, between 1840 and 1860. Up to 1830 or 1840, the movement had been growing steadily; after the Civil War, the membership fell off noticeably and continuously; somewhere in between the two dates something had happened. The summit had been reached; the descent had begun." [2]

The Shakers, officially known as The United Society of Believers, reached its peak of membership in the decade 1850 to 1860, during which period it had a total membership of 5000 to 6000 persons in the 18 or 19 societies. More than three times that number of persons had come under Shaker influence for longer or shorter periods of time. The Shakers owned, at this time, about 100,000 acres of land. Most of it had been properly cleared, fenced, and tilled or grazed. Each community had substantial buildings for dwellings, meetings, schools, shops, sheds, and barns.

Whence Came the Shakers?

The Shakers were organized in England about 1747 by a small group of dissenting Quakers, who believed that worship should be a time of active, exhilarating movement, dancing, singing, shouting, and the like. It is not unlikely that these ideas were borrowed from the Camisards or "French Prophets" who were then exiled in England, banned from France because of their war against the state Church. "Camisards" was the name given to the Protestant peasants who formed a part of the romance-speaking people of France, and who were regarded as the nursing ground of mediaeval heresy. These people experienced miracles, were guided by strange lights, heard the songs of strange voices, were unharmed by bullets, wounds, and falls. The supernatural was a part of the life they led.[3]

Ann Lee became a member of this group of dissenters in 1758, and was made its leader in 1770. She was the daughter of poor parents and, since there were no schools for the poor, she could not read or write. Nevertheless, she was an extremely sensitive, spiritually minded person. She regarded herself as a natural celibate but, according to custom, had married. Four children were born to this marriage but all died in infancy. Ann regarded the loss of her babies as a

2. Melcher, Marguerite Fellows, *The Shaker Adventure*, 1941.
3. *Encyclopedia Britannica*, 1929, vol. 4, 14th ed.

punishment for her sensualism. Among other things she held to the belief that "the life of the spirit demands a celibate life".[4] She was thrown in jail and much abused for her preachments. In 1774, she gathered eight faithful followers around her and set sail for America, landing in New York in August of that year.

This was a period of exciting anti-British feeling in the colonies and these Shakers were regarded as spies and thrown in jail for a time. With no place to settle, the party scattered and lived apart until 1776. During this year, they gathered at Viskeyuna, New York, seven miles from Albany, and there built a log cabin. From this humble beginning, Shakerism grew and developed. Eventually, the sect became a small but a prosperous, well-ordered, respected segment of early America.

There was much interest in religion during these days in colonial America. Religious revivals were common and the zealous proponents of Shakerism soon made converts in New York, New England, and the Southwest. The first of the Shaker societies was the one at Mount Lebanon, New York, which was, for a long time, the largest. It became the head society in that all of the societies followed its lead in religious matters and other activities. Edicts and pronouncements issued from the central ministry of the Mount Lebanon society were faithfully observed by the other communities. This resulted in a great similarity within the various colonies. Each, however, operated as a separate economic unit. The Ministry of the Mount Lebanon society made regular and frequent visitations to the other societies. By this plan, all were made aware of not only the problems but the progress and advancements in all the other communities. Hence, the great solidarity and uniformity in the developments in agriculture, animal husbandry, architecture, manufacturing, and other industries.

Opposition to the Shakers

The term "Shakers" is regarded as a vulgar contraction of "Shaking Quakers," the name given to the new sect because of their fanatical form of worship which included not only marching, dancing, and singing, but violent body movements at times, all of which were regarded as blasphemous. Added to this was Ann Lee's insistence on

4. *Kentucky Progress Magazine 5*, No. 4, 16 (1933).

the principle of celibacy as the way to spiritual purity and her assumed role of the second Christ embodying the female element of the divine nature as Jesus had the male element. Furthermore, she proclaimed the imminence of the millenium. The preachings of Ann aroused strong resentment to the sect both in England and America.

Shaker societies, both in New England and in Ohio, suffered much at the hands of "outsiders". In Massachusetts, the early missionaries were stoned and beaten but faced persecution with great Christian faith. At Union Village, Ohio, the society suffered greatly by having its buildings burned, fences torn down, and crops destroyed. Eventually, however, the Shakers won the confidence of their neighbors and were accepted for their honesty, integrity, and hard work. Their strange religious practices were apparently never understood but tolerated.

Foundations of Shaker Success

The basic activity of the Shaker system was agriculture. The first aim was to supply the needs of the Society. Production in excess of this could be sold to the outside world. In time, the Shakers became successful producers of all useful crops, fruits, vegetables, herbs, and even medicinal plants. At the same time, many industries, mainly out of necessity, were developed. Saw mills, grist mills, furniture and implement making, weaving, and other industries in time, became parts of each successful, self-supporting colony.

In due time, the Shakers established an enviable reputation as skilled workmen and honest merchandisers. Their garden seeds became famous and were sold widely throughout the country. Likewise, their shoes, harness, woven cloth, hats, bonnets, and other items were in demand. The quality of the Shaker workmanship and the things they made has been attributed not alone to their integrity but to their sense of security, both for this life and for eternity. It is said that no inferior product ever came from the hands of a Shaker. Would that that spirit prevailed more generally among us today!

In associating the coming of the Shakers with the Revolutionary War period, Guthe says, "Those were turbulent times. . . . The Shakers are one of a number of socioreligious organizations, founded on sincere convictions, which developed during this interesting period." [5]

5. Guthe, Carl E., *House and Garden 87*, 103 (March, 1945).

Garrison, in referring to the Shaker movement, says, "The religio-social system included: celibacy; communism; separation from the world; centralized theocratic control of each community by the central ministry; equal eligibility of men and women to places of authority; plain living and hard work." [6]

The Drug Industry of the Shakers

It is a well-established fact that the Shakers were pioneers in collecting, drying, and packaging native herbs for both culinary and medicinal uses. They also cultivated those plants that were in short supply. Furthermore, they processed those drug plants that were used for the manufacture of extracts, fluid extracts, volatile oils, distilled flavoring and fragrant waters.

In their twelve-page *Annual Wholesale Catalogue*, the United Society of Believers, at Union Village, near Lebanon, Ohio, under the date of 1850 lists seven classes of drug plants and drug plant products as follows: [7]

(1) 251 drug plants, various parts

(2) 46 extracts

(3) 8 inspissated juices

(4) 15 essential oils

(5) 4 pulverized sweet herbs

(6) 7 double distilled and fragrant waters

(7) 31 powdered roots, herbs, barks

The price per pound is given for all items in groups 1 to 6 in the list above. Those items in groups 1 to 5 are listed by both their common and botanical names. Those of us who are older will remember when the burdensome task of preparing for the State Board examination was that of learning long lists of Latin titles, synonyms, parts used, habitats, and chief constituents of plant drugs.

The common names in the Catalogue "are such as are in use in the cities of Cincinnati, St. Louis, Louisville, New Orleans, etc. The

6. Garrison, W. E., *Christian Century 58*, 530 (April 16, 1941).

7. *Annual Wholesale Catalogue:* Herbs, Medicinal Plants, Extracts, Essential Oils, etc., 1850, Union Village, Ohio.

Botanical names are from Eaton's Manual of Botany, Griffith's Medical Botany, and Raffinesque's Medical Flora." [8]

Manufactured Medicinal Products of Shakers

Shaker interest in herbs and medicinal plants can be traced to about 1800. The manufactured products are mentioned around 1820 to 1830. From the latter date, the Shaker drug industry developed rapidly, especially at the Mount Lebanon, N. Y., colony. By 1850, it is evident that the Union Village, Ohio, drug industry was also of considerable importance.

During the early years of the Shaker movement, there were no legal restrictions applicable to the practice of pharmacy. It is rather surprising, however, that the Shakers developed their herb and drug industry into one of their most successful enterprises. Almost all of the writers about the Shakers mention their herb and drug industry but none of them give details about it. There is very little mention of the Shakers in our pharmaceutical literature. Except for the Wholesale Drug Catalogue, previously mentioned, and a few Shaker Almanacs, very little original literature on this subject has been available for the writer.

Since the Shaker societies were self-sufficient in most practical respects, it is not strange that they developed a system of medicine to suit their needs. Thomsonianism was a popular medical system of that period and suited the pioneers, as it did the Shakers, rather well. The Shakers did not hesitate to call in doctors from the outside when necessary, but believed that their regimen as to wholesome food, reasonable amount of work and rest left no cause for illness. Many of the Shakers lived to a ripe old age.

It appears that the Shakers pioneered or at least contributed much to the manufacture of our pharmaceuticals such as extracts, inspissated juices, essential oils, distilled and fragrant waters, and other products. It was the policy of the Shakers to do their assigned tasks well. For this reason, they could, in sincere good faith, proclaim the merits of their products in all confidence.

In support of this statement, a quotation from the Annual Wholesale Catalogue of Herbs, Medical Plants, etc., which is directed to "Our Patrons" is given here: "The articles contained in the follow-

8. *Op. cit.*

ing catalogue are prepared and put up with greatest care and fidelity. The various Herbs, Roots and Barks, are gathered in the season proper to each; the stalky and coarser part being rejected; they are then uniformly dried under shelter, after which they are neatly prepared and papered in assorted packages for the convenience of the purchasers.

"Our Extracts are prepared by experienced persons; they are vaporized by steam, and great care is used that they are not burned, or otherwise injured. Our Inspissated Juices are of superior quality and excellence.

"We pledge ourselves that our preparations shall be inferior to none offered in market, and that they shall be such as will meet the approbation of dealers and practitioners generally, to whom we confidently recommend them.

"Orders for such Native Plants as are not in the Catalogue will receive due attention."

The merchandising acuity of the Shakers is exemplified by the following advertising statement which appears at the end of the page which contains the above quotations.

"Druggists, Merchants and others who desire Garden Seeds, will be allowed a commission of 33 per cent. We can supply them at the proper season of the year, with an excellent assortment, for esculent vegetables, *fresh* and *genuine:* and which for quality, are unsurpassed in any section of the Union.

"It would be well to send orders as early as the middle of November, in order to secure a full and complete variety." [9]

Manufacturing Processes and Procedures

It is unlikely that the Shakers invented many of the pharmaceutical manufacturing processes and procedures, but they undoubtedly improved on them. As is common with manufacturers, Shaker details of procedures are not revealed, at least so far as the writer knows, so it may be assumed that the orthodox procedures of the day were generally followed. It is known that, in some instances, the fresh drugs were artifically dried at low temperatures, but no method of drying the inspissated juices has been mentioned. Likewise, it is not clear whether the Shaker extracts and fluid extracts were made

9. *Op. cit.*

by the percolation method from dried crude drugs, with subsequent evaporation and concentration, or by properly concentrating the expressed juices of fresh drugs.

The Vacuum Process Controversy

By 1850, the herb and drug industry had grown to rather large proportions. This business had grown in a like manner in the outside world. The Tilden Company had been organized around 1847 in Mount Lebanon, N. Y., close by the Shaker society. In speaking of the drug industry, John Uri Lloyd said that "with the Tildens were associated the Shakers of Mount Lebanon, N. Y. Hand in hand did they work, their efforts uniting to the up-building and progress of the great Tilden establishment, described by Professor William Procter in the American Journal of Pharmacy, 1855, as an industry exhibiting wonderful pharmaceutical activity".[10]

In following up the editorial of the *American Journal of Pharmacy*, it appears that the question of priority of invention or first use of the vacuum process in the making of extracts had arisen between the Tildens and the Shakers. Each claimed to be first in the use of the vacuum process. This poses an interesting question. The Tilden Company was established around 1848.[11] The Shakers had been making extracts for more than 20 years and had developed an interesting vacuum apparatus. Its simplicity exhibits a practical inventiveness on the part of the Shakers and is described as follows: "This consists of a globular copper vessel supported on cast iron columns attached to the floor, about the size of an ordinary sugar vacuum pan. The bottom is jacketed for applying steam heat, whilst there is an interior false top extending from the sides up nearly to the manhole at top, which prevents the vapor which may condense on the interior of the proper top from falling back into the bowl of the evaporator. They, at present, have no steam engine, but use a peculiar arrangement for exhausting the air from the pan, which consists in attaching the condensing vessel to a vertical tube 30 or 40 feet high, in which a column of water is constantly and rapidly descending, the effect of which is to produce a constant suction, of sufficient force to keep the evaporator sufficiently exhausted." [12]

10. Lloyd, John Uri, *J. Am. Pharm. Assoc. 8*, 605 (1919).
11. Kremers, Edward and Urdang, George, *History of Pharmacy*, 1951.
12. *Am. J. Pharm. 18*, 90 (1852).

Later, in commenting on Shaker's Extracts, the editor of the *American Journal of Pharmacy* said, "The Society of Shakers have long been engaged in the preparation of medicinal extracts, in connection with their other business of collecting medicinal plants, and the amount of their extracts consumed annually is, if we are rightly informed, very considerable; hence any improvement that can be affected in their processes will be a general benefit, to the extent of the consumption. In a recent number we noticed several of the products of the Messrs. Tilden & Co., and referred to their having introduced the vacuum apparatus, on a large scale, in the manufacture of extracts. Following the example of these gentlemen, the Society of Shakers have provided their laboratory with a vacuum evaporator, and the extracts now submitted to our notice are a portion of its first fruits." [13]

The Shakers denied any knowledge of the vacuum process being used to prepare medicinal extracts, other than by themselves. They said, "We adopted the vacuum pan as a necessary item by the recommendation of several members of the New York College of Pharmacy, whom we consulted on the occasion." [14]

The writer does not know how this controversy was settled but will quote what appears to be the Tilden & Co. rebuttal to the preceding Shaker statement. Messrs. Tilden say that "while our manufactory was in process of erection, members from the family of M. Fowler (Shakers) visited our works, and knew we were engaging in the manufacture of extracts by a 'new process' because they saw the apparatus, and made inquiries in regard to it and our manipulations, both before and after the erection of *their* apparatus, which occurred in the summer of 1850." [15]

According to Hoffman, "The Shakers propagated medicinal plants as early as 1825, long before such cultivation became widely spread in the United States. They also devised the famous system for taking down medicinal extracts 'in vacuo' and their vacuum apparatus was a model for the great medicine industry of today. The Shakers first pressed herbs into small packages, and have sold as much as seventy-five tons of drugs, made up in small ounce packages, in one year." [16]

13. *Ibid.*, p. 93.
14. *Ibid.*, p. 90.
15. *Ibid.*, p. 188.
16. Hoffman, George Niles, *Pharm. Era 53,* 197 (1920).

Credit to Whom Credit Belongs in the Drug Industry

In the thinking of most of us, the drug manufacturing industry in this country was almost unheard of until after the Civil War. On the other hand, the Shakers had approached the peak of their herb and drug industry prior to this time. It may be proper to suggest also that it was during this period that pharmacists in the eastern seaboard area complained about the importation of spurious drugs and so-called patent medicine. The situation became so serious that a meeting to discuss the problem was convened at the New York College of Pharmacy in September 1851. The most important outcome of this meeting was that it was agreed to call a second meeting in Philadelphia in October 1852. The American Pharmaceutical Association was organized at this meeting.

The prosperous drug industry of the Shakers may have thrived indirectly on the imported patent medicines because these products were imported from England and the Shakers were exporting herbs and extracts to London and elsewhere. This may be idle speculation for soon thereafter the Shaker drug industry dwindled and the patent-medicine business of the domestic variety flourished. However, some support to this idea may be found in the words of Sister Marcia Bullard. Among other things about Shaker herbs and medicines, she says, "We had big beds of sage, thornapple, belladonna, marigolds, and chamomile as well as yellow dock, of which we raised great quantities to sell to the manufacturer of a well known 'sarsaparilla'.

"We also made a sarsaparilla of our own and various ointments. In the herbshop the herbs were dried and then pressed into packages by machinery, labelled and sold outside. Lovage root we exported both plain and sugared and the wild flagroot we gathered and sugared too. On the whole there was no pleasanter work than that in the 'Medical Garden' and 'herb shop'." [17]

Several of the Shaker societies developed a drug industry. The largest medicinal herb and drug industry was that of the parent Shaker society at Mount Lebanon, N. Y. According to Andrews, this industry was established around 1800, "being the oldest of its kind in the country." [18] While the Shakers were the first in America to introduce botanical medical practice, their products were not offered for sale until about 1820.

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17. Bullard, Sister Marcia, *Good Housekeeping 43*, 33 (July 1906).

Records of the sales of Shaker drugs and medicines began to appear in 1825. From this time on, the herb and medicinal products sales increased from year to year. Herbs were not only shipped to domestic customers but to Paris, London, and elsewhere abroad. The growth of the business is indicated by the pounds of products marketed. In 1831, about 4000 pounds were sent to the market; 6000 pounds in 1836; 16,500 pounds in 1849. The demand for the Shaker herbs and extracts so increased that it became necessary for the Mount Lebanon society to purchase large amounts of herbs, roots, etc., from outside sources. And many of these came from abroad.

As early as 1832, this Society was compelled to build a large "herb house" in order to take care of the increasing drug business. Expanded facilities were especially needed because of the growing demand for extracts, syrups, ointments, and other pharmaceutical products.[18] In addition to the staple herb and medicinal items, there was an ever increasing demand for new and miscellaneous products.

Tools and Equipment Increase Drug Manufacturing

The Shakers invented the tools and equipment needed to expedite work in many phases of their industrial program. A steam boiler on a globular-shaped copper vacuum pan was installed in 1850 for drying herbs. Power drug presses made it possible to compress 21,000 pounds of herbs in 1850. Double this amount was pressed three years later with the aid of added equipment. During these same three years, the pounds of extract were increased from 7000 to 7500.

During 1861-62, more than 100 different solid and fluid extracts were not only manufactured but packaged in amounts of one ounce to five pounds. In 1862, more than 6000 pounds of solid extract were prepared. This product increased to more than 16,000 pounds in 1864. In the period 1860 to 1867, more than 7000 pounds of pulverized roots and herbs were produced. During this period, the production of many other medicinal preparations also increased. According to Andrews, extracts of mandrake and colocynth were made as late as 1900, "and the industry survives today in the preparation of the famous Norwood's Tincture of Veratrum Viride."[19]

18. Andrews, Edward D., *New York State Museum Handbook 15*, pp. 87-109.

19. *Ibid.*

"The Shakers pioneered in developing a machine for filling seed bags. And they were the first people to package seed commercially. They had a tremendous business in medicinal herbs, and they created a package filler and label press . . ." [20] However, as the business increased, labels, paper boxes, and even paper bags were purchased from commercial suppliers.

Medicines the Shakers Advertised

On the inside cover page of the Annual Wholesale Catalogue of Herbs, Medical Plants, etc., previously mentioned, more than half of the page is devoted to flattering testimonies concerning certain products made at Union Village, Ohio. One of the preparations is Compound Fluid Extract of Sarsaparilla. One testimonial reads, "I have the pleasure of saying that I have used the extract of Sarsaparilla, the Hybrid Colocynth and the Belladonna, prepared at Union Village by A. Babbit & Co., and that I have never found better articles of the kind. From the fidelity with which these articles are prepared and vended by them, are of prime quality, and may be fully relied on.

Cin. Dec. 18th, 1849. R. D. Mussey
Prof. Surg'y Medical College, Ohio" [21]

Shaker Extract of Roots or Mother Seigal's Curative Syrup is described in "The Story of an Accidental Discovery in a Shaker Almanac." Much discussion of family diseases is given along with many testimonials.[22]

"The Mystery Explained" is contained in the Shaker Almanac for 1886. Much space is given to Shaker Extract of Roots or Seigal's Syrup; Shaker Family Pills; Shaker Soothing Plaster and Pain King.

Inside the front cover page is a good picture of Shakeresses labelling and wrapping the bottles containing the Shaker Extract of Roots or Seigal's Syrup. In the upper right-hand corner of page 30 is a picture of Alonzo Hollister, the famous chemist, concentrating the Shaker Extract of Roots or Seigal's Syrup, in vacuum pan, Mount Lebanon, N. Y.

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20. *House and Garden 87, 37* (March 1945).

21. *Annual Wholesale Catalogue:* Herbs, Medical Plants, etc., Union Village, Ohio, 1850.

22. *New Favorite Cooking Receipts of the Shakers and Illustrated Almanac for 1883.*

At the top of the inside back cover page are two advertisements:

1. *Shaker Extract of Roots*

"For fifty years the Shakers have been studying roots, barks, herbs, and plants, and learning how to extract the most available essences for the cure of disease. The result is that they know how to make the very best preparations in the world. The triumphs of 'Shaker Extract of Roots' are on record for the benefit of suffering humanity. Be wise and use this unfailing remedy."

2. *Shaker Family Pills*

"These pills are not only handy to have in the house, but they operate so gently and surely yet without straining or distressing the bowels, that no family can afford to be without them. They break colds and fevers, and do away with bilious disorders. People who use them once accept them as the best Cathartic Pill in the world." [23]

"The Mystery Explained" is retold in a 32 page pamphlet of Shakers Good Cooking Receipts along with advertisements of Shaker medicines and testimonials. Advertisements are found on the inside of the back cover page as follows:

1. *Shaker Soothing Plaster*

"A cure for pains in the back and sides. The Soothing Plasters afford immediate relief.

"Our Porous Plasters never get dry, because the linen of which they are composed is covered with India Rubber. They refresh the system and banish aches of every kind. This is why they are called 'Shaker Soothing Plasters'.

"If you are troubled with a cough, with a pain in the chest, use the Shaker Soothing Plasters."

2. *Prices of Shaker Medicines*

"Shaker Extract of Roots, or Seigal's Curative Syrup	per bottle	60¢
Shaker Family Pills	per bottle	25¢
Shaker Soothing Plasters, each		25¢

"In case the reader cannot obtain the medicine from a local dealer, we will forward the same by express, on receipt of P. O. Order, or

23. *Shaker Almanac*, "The Mystery Explained", 1886.

stamps in a registered letter, for the quantity required. Agents wanted where we have none. Send for terms. Address A. J. White, 168 Duane Street, New York. For Sale by all Druggists and Dealers in Medicines generally."

3. *Shaker Family Pills are again described but differently*

"Unlike many kinds of cathartic medicines, do not make you feel worse before you feel better. . . . Shaker Family Pills prevent ill effects from excess eating or drinking. A good dose at bedtime renders a person fit for business or labor in the morning.

"The pills being sugar coated, are pleasant to take. The disagreeable taste common to most pills is obviate."

4. *Kaskine* (The new Quinine)

"No bad effect, no headache, no nausea, no ringing ears, cures quickly. Pleasant. Pure. A Powerful Tonic that the most delicate stomach will bear. A specific for Malaria, Rheumatism, Nervous Prostration and all *germ diseases*. Kaskine Co., 168 Duane Street, New York." [24]

Shaker Medicine Cabinet

In the issue of *Life*, March 21, 1949, there is an interesting illustrated account of the Shakers. The pictures portray people, plans, furniture, and other objects. Among them is a picture of a Medicine Cabinet covering the space of a page but is divided in the center so as to mar its effectiveness.

This Cabinet has five shelves on which are 52 bottles of varying sizes mostly glass stoppered and plainly labelled. Among the readable labels are: Tinct. Green Soap; Rose Water; Guaiac; Tinct. Nux Vomica; Wine Ipecac; Tinct. Myrrh; Oil Peppermint; Wine Colchicum; Clove Pulv.; Essence Peppermint; Tinct. Camphor; Tinct. Digitalis; Lovage Ess.; and others.

Each Shaker Society, we are told, had a medicine cabinet of some kind. This particular cabinet was the property of the Canterbury, N. H. colony. "The Shakers never banned doctors, but because doctors were scarce they made or invented their own remedies and sometimes marketed them widely." [25] The Canterbury, N. H., Shaker

24. *Shaker Good Cooking Receipts*, "Pamphlet", 1889.
25. *Life*, "The Shakers", 26, 142 Ill. (March 21, 1949).

colony, at one time, did a great herb medicine business. In 1914, it was reported that "the only medicines the Shakers still make are witch-hazel and sarsaparilla".[26]

In "A History of Pharmacy in Pictures," by George A. Bender, which has appeared in *Modern Pharmacy*, is number 26, "The Shakers and Medicinal Herbs," by Robert A. Thom. The Shakers are portrayed as they were about 1830. In this picture, Mr. Bender plays the part of a good Shaker brother by bringing in the herbs for the Sisters to process and package.

This picture is an interesting and instructive portrayal of the herb industry of the Shakers. The two page story, "The Shakers and the Herb Industry," accompanying the picture, tells much of the work of the "Believers" with herbs and medicinal drugs. Five good pictures show: 1. The Crushing Mill; 2. The Herb-House-1855; 3. Finishing Room in the Herb House; 4. Hydraulic Press; and 5. Laboratory in the Herb House. These leave an impression of a well-organized and managed drug business in our country a century or more ago.[27]

Why Did the Shakers Vanish?

To write a paper as incomplete as this one about a segment of early America as remarkable as the Shakers has brought me almost to the brink of an apology. To learn of this remarkable sect has impressed me profoundly.

In speaking of the Shakers, Melcher says, "The Shaker adventure offers an interesting disproof of the claim made by modern big business that the profit motive underlies all progress. The Shaker communities were a practical demonstration that competition is not necessarily the motivating force either of business success or of improved standards of living. Nothing they made was made primarily for profit." In speaking of the legacies left by the Shakers, Melcher continues, "One of the intangible legacies the Shakers left to the world is their demonstration that it is possible for man to create the environment and the way of life he wants, if he wants it enough. Men can choose. In a world of defeatism this is a cheering thought."[28] Other legacies suggested by Melcher are self-control, exemplified by their practice of strict celibacy; tolerance, in the face of ill treatment by bigots of other

26. *Outlook*, "The Spectator", 196, 40 (Jan. 1914).
27. Bender, George A., *Modern Pharmacy*, No. 2 (1955).
28. Melcher, Marguerite Fellows, *The Shaker Adventure*, 1941.

sects; confidence and courage, in the face of difficulties. They abolished poverty in their own communities. By a strict regime of living, longevity among the Shakers was greater than it was for those "out in the world". They built their own practical utopia in an imperfect and impractical world.

Well, you may ask, why did the Shakers vanish? A wholly satisfactory answer is not forthcoming. In discussing life among the Shakers, Carr writes, "It is surely no convent life with rigid laws and penances; no dark vaults or gloomy cells; no high walls or grated windows. Strong willing hearts are there, bearing a firm but a gentle rule. A ready obedience from all gives birth to the good order and happiness that are plainly visible." [29]

It is evident that Shakerism began to decline after the Civil War. This may be attributed to many things. It seems that their missionary effort lost its zeal in this period and their exciting religious customs were dropped because the members had become old and inactive. The consequences of celibacy were in evidence even though the Shakers continued the policy of adopting orphans. It is likely that the social changes following the war were attractive to young Shakers who were privileged to leave the society at any time. The rapid industrialization of the country lessened the demand for their hand-made articles. These are but a few of the explanations given for the passing of the Shaker sect. Their "industry, good workmanship, shrewd but honest and blameless private living had won the esteem as well as the patronage of their neighbors", according to Garrison. And, in speaking of the Shaker experiment, he says, while it lasted, "it was the most successful experiment in religious communism that this country ever saw." [30]

29. Carr, Mary F., *Life Among the Shakers* (Booklet about 1880).
30. Garrison, W. E., *Christian Century 58*, 530 (April 16, 1941).

ABSTRACT

The Role of Vitamin K in Cellular Growth. Brodie, A. F., Russell, P., and Kashket, E. Presented before the Division of Biological Chemistry of the American Chemical Society in New York City, April 7, 1960. The role of vitamin K as a coenzyme in the respiratory process of living cells was reported by the authors from studies on a bacterial system. It was found that vitamin K apparently acted by transferring electrons to and from other vital compounds involved in oxidative phosphorylation, the process through which cells are able to store energy. Such energy-rich compounds then provide the cell with the fuel needed to build its constituents.

When the cells were deprived of vitamin K, they were no longer able to use oxygen in the normal way to break down foodstuffs but continued to grow through a fermentation process which has been observed in cancerous tissue in mammals. The authors postulated that this finding might ultimately be helpful in developing compounds capable of blocking cancer growths.

The bacterial system used in these studies had the advantage that it could be chemically separated into a number of parts which were inactive by themselves but active when recombined. The necessity for vitamin K was found by studying the components of this system and by taking advantage of the sensitivity of vitamin K to light, by which mechanism it was possible to destroy vitamin K in the bacterial system and thus show the requirement for it.

The authors also reported that they isolated a naturally occurring naphthoquinone from the bacterial system, which closely resembled vitamin K, and was believed to be an intermediate of vitamin K.

BOOK REVIEWS

Methoden der Organischen Chemie, (Houben-Weyl). Volume 1, Part 2. Allgemeine Laboratoriumspraxis II. Edited by Eugen Müller. 1017 pages, with 680 illustrations. Georg Thieme Verlag, Stuttgart, 1959. DM 196 ($46.65).

Part 1 of Houben-Weyl's treatise on "Laboratoriumspraxis" was earlier reviewed in this Journal, Volume 130, page 427, 1958. Part 2, the subject of this review, is a companion volume to the former book. The subject coverage of Part 2 is as follows:

Comminution, Sieving, Sifting, Particle Size Analysis (58 pages)
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Methods of Producing Vacuum; Operating under Reduced Pressure (60 pages)
Heating and Cooling; Measuring, Recording, and Regulating Temperature (141 pages)
Properties and Purification of Important Organic Solvents (100 pages)
Drying Agents (13 pages)
Prevention of Accidents; Carcinogenic Substances (52 pages)

This volume is another noteworthy contribution to the Houben-Weyl series.

ARTHUR OSOL

Modern Pharmacology and Therapeutics. Ruth D. Musser and Joseph G. Bird, xiv + 828 pp. The Macmillan Company, New York, N. Y. 1958. Price: $6.75.

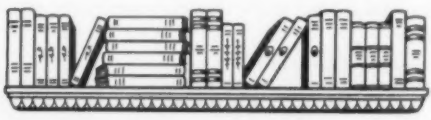
While it is essential for all members of the medical professions to have some knowledge of pharmacology, the degree of familiarity with this subject varies with each individual profession. With this thought in mind, Mrs. Musser and Dr. Bird have written an excellent text for use by the nursing student studying pharmacology.

The first section of this text is devoted to basic material such as explanations of the nature and sources of drugs, the prescription, drug standards and legislation, and the sundry types of dosage forms of pharmaceutical agents. Also in this section are included excellent chapters on pharmaceutical mathematics and methods of administering drugs. Sections II through XI are concerned with the etiology and pathogenesis of diseases and maladies afflicting the human body and the drugs used in the treatment and correction or ablation of these disorders.

Although this text does not offer great detail, it is, nevertheless, complete and concise in its discussions of the divers topics presented. Some of the outstanding features of this book are the tables of drugs used in different disorders and the doses of these drugs, the review questions at the end of each chapter, the table of poisons and recommended treatments, and a well-rounded glossary.

Modern Pharmacology and Therapeutics serves as a ready source of pharmacologic and pharmaceutical information for all medical professions and can be considered as one of the foremost texts available for the nursing profession.

E. E. Vogin



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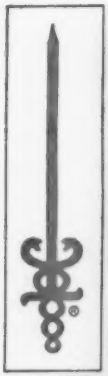

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